Public Health Goal for
GLYPHOSATE
in Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the

information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 1,000 ppb is developed for glyphosate in drinking water. California's and U.S. Environmental Protection Agency's (U.S. EPA's) Maximum Contaminant Levels (MCLs) are 700 ppb based on systemic toxicity (renal tubular dilation) in a three-generation rat reproduction study with an NOAEL of 10 mg/kg-day. Glyphosate is a non-selective systemic herbicide used in agriculture, rights-of-way and aquatic systems. Exposure to glyphosate may occur from its normal use due to drift, residues in food crops and from runoff into potential drinking water sources. Following acute exposure, glyphosate has low systemic toxicity to mice and rats. In humans, irritation of the oral mucous membrane and gastrointestinal tract is the most frequently reported effect in suicide attempts with glyphosate-surfactant formulations. In most of the short-term and long-term toxicity studies, there were no treatment-related gross or cellular changes except reduced body weights and increased liver weights at relatively high doses. After a thorough review of the available studies, the U.S. EPA classified glyphosate as a Group E carcinogen (evidence of noncarcinogenicity for humans). Glyphosate is not mutagenic or teratogenic and there is no evidence for reproductive toxicity in multigeneration studies in rats. We consider the results from a rabbit teratology study with a no-observed-adverse-effect level (NOAEL) of 175 mg/kg-day for maternal toxicity (diarrhea and mortality) as the appropriate basis for toxicological evaluation in humans. Based on these data, OEHHA has developed a PHG of 1.0 mg/L (1,000 ppb) for glyphosate in drinking water, which is higher than the federal MCL of 700 ppb.

INTRODUCTION

Glyphosate, the isopropylamine salt of N-(phosphonomethyl) glycine, is a non-selective post-emergence herbicide for controlling weeds in agriculture (cropped and non cropped), forestry, rights-of-way and aquatic systems. At low doses, it is used as a plant growth regulator. It is sold under various trade names such as Roundup®, Rodeo® and Accord®. The major product is Roundup®, which is formulated as 41% of the isopropylamine salt and 59% inert ingredients. It is sprayed as a liquid with ground and aerial equipment. Because of its extensive use (18.7 million pounds annually) under various conditions, there is a potential for occupational exposure via the dermal route and for exposure to the general public via food and water (U.S. EPA, 1993).

The California Department of Health Services (DHS, 1989) conducted a risk assessment on glyphosate and set the Proposed Maximum Contaminant Level (PMCL) and MCL for drinking water at 0.7 mg/L (700 ppb). This was based on systemic toxicity in a three-generation rat reproduction study with an NOAEL of 10 mg/kg-day. This is the same as the proposed U.S. EPA MCL of 0.7 mg/L based on the same three generation rat reproduction study, allowing a 20% relative source contribution (RSC) from drinking water (U.S. EPA, 1992).

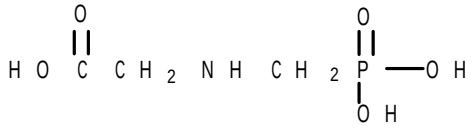
There are only a few published health effects studies on glyphosate in the past few years. The majority of the available studies on glyphosate were conducted by the Monsanto Company for the registration of glyphosate as a pesticide. Therefore, many of the studies meet the testing requirements of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines. These studies have been reviewed extensively by Trotter *et al.*, 1991; U.S. EPA, 1992 (Drinking Water Criteria document); U.S. EPA, 1993 (Registration Eligibility Decision document); Smith and Oehme, 1992; the California Environmental Protection Agency (Cal/EPA), 1992; and more

recently by the World Health Organization (WHO, 1994). This document provides a brief summary of relevant toxicity studies.

CHEMICAL PROFILE

The properties of glyphosate are summarized in Table 1.

Table 1. Physical and Chemical Properties of Glyphosate (WHO, 1994; Edmund, 1988)

Name	Glyphosate (N-(phosphonomethyl)-glycine)
Trade names	Roundup®, Rodeo®, Accord®
CAS No.	1071-83-6
Physical state	white crystalline solid
Molecular weight	169.07
Structure	
Density	0.5 g/ml
Solubility in water	12 g/L at 25^0C
Solubility in organic solvents	insoluble
Vapor Pressure	$7.50x10^{-6}$ mm Hg at 25^o C
Henry's Law constant	$1.39x10^{-10}$ atm-m^3/mol.
Octanol-water partition coefficient (Log K_{ow})	-2.8
pKa's	2.32, 5.86, 10.86
pH (1% solution in water)	2.5

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Soil

Glyphosate may reach soil in its normal use as a liquid spray, through spillage or accidental discharge. Once in soils, it is strongly adsorbed onto the soil forming insoluble complexes with metal ions. The estimated half-life in soil is 60 days. After 360 days, residue levels were 6 to 18% of the initial applied dose (Feng and Thompson, 1990). Precipitation, soil composition, presence and absence of a soil constricting layer and drainage type may influence the leaching of glyphosate from soil. Field and laboratory studies indicate that glyphosate generally does not move vertically in the soil below the topmost six inch soil layer (U.S. EPA, 1993).

Air

There are no data available on ambient air concentrations of glyphosate.

Water

Glyphosate may enter water via runoff, from overspray, or from spray drift. In water, it adsorbs strongly to sediment and particulate matter in the water column. It may also form insoluble complexes with metal ions and precipitates. Sediment adsorption and biodegradation represent the major dissipation processes in aquatic systems (Goldsborough and Brown, 1989). The half-lives of glyphosate in three forest ponds in Manitoba, Canada that were aerially sprayed in August were approximately 1.5 to 2 days; glyphosate was not detected in any sample by day 38 (Goldsborough and Brown, 1989).

The off-target movement of glyphosate was studied (Smith *et al.*, 1996) at three different sites (Western Avalon, Massey Drive and Oxen Pond) in Newfoundland, Canada wherein a 2% solution of Roundup® was sprayed evenly at the rate of about 11.4 to 13 L/hectare. Two sites (Massey Drive, and Oxen Pond) were sprayed twice while the third (Western Avalon) was sprayed only once. Western Avalon, and Oxen Pond sites had low-permeability soil layers. The Massey Drive site was located on a fractured lime stonebed. Drinking water wells from sprayed sites were sampled at 1, 2 and 4 weeks after the first spray and at 1, 2, 4, 13 and 32 weeks after the second spray. Glyphosate was detected in well water at the Massey Drive site at levels ranging from 0.0072 to 0.045 mg/L. Levels peaked two weeks post-spray at 0.025 mg/L in well water and then dropped off to 0.004 mg/L by the fourth week of sampling. After the second treatment, the concentration in the well increased to a maximum of 0.045 mg/L at seven weeks post-spray and again dropped off. Glyphosate is known to adsorb strongly to soils, but this factor alone did not prevent off-target movement of glyphosate on a limestone bed where the topsoil was replaced with gravel, and thus the potential for off-target movement of chemical was high.

Food

Glyphosate is not absorbed by a plant's root system because of its strong adsorption to the soil. However, it is easily absorbed by leaves from spray residues and is translocated throughout the plants and fruits. Therefore, glyphosate concentration may increase in plants immediately after spray. Ingestion of sprayed food material or products from animals fed contaminated vegetation may lead to glyphosate exposure. In its dietary risk assessment based on a worst-case scenario, U.S. EPA (1993) concluded that the chronic dietary risk from food use is minimal. The calculated theoretical maximum residue contribution for the U.S. population is 0.025 mg/kg-day. The exposure for the most highly exposed subgroup, non-nursing infants less than one-year-old, is 0.058 mg/kg-day. The major dietary contribution is from wheat products.

Human exposure to glyphosate might occur in the occupational setting during spraying, mixing and cleaning. Estimated worker exposures for spraying with boom, handgun and backpack were 272, 7,959 and 3,620 µg/hour (U.S. EPA, 1993).

METABOLISM AND PHARMACOKINETICS

The absorption of glyphosate from oral administration in various species is about 30 to 36%. The absorbed dose is mainly eliminated in the urine and feces as the parent compound. In a recent single dose (5.6 or 56 mg/kg) study in F344 rats (NTP, 1992), 30% of the oral dose was absorbed. Analysis of the tissue distribution indicated that most of the radioactivity was in the gastrointestinal tract and only 1% of the dose remained in the tissues after 24 hours. In a comparable study, after a

single oral dose of 10 or 1,000 mg/kg body weight, 30 to 36% absorption was reported based on percentage excretion in the urine. The remaining total body burden was about 1%, which was widely distributed in the body but mainly associated with bone (Monsanto, 1988 as cited by WHO, 1994). The dermal absorption from diluted Roundup® in Rhesus monkeys was about 5.5% after 12 hours of exposure (Wester *et al.*, 1991).

Glyphosate is poorly metabolized. Aminomethylphosphonic acid (AMPA) is the only metabolite found in feces and accounts for 0.2% to 0.3% of a 10 mg/kg administered dose (Brewster *et al.*, 1991). After a single oral dose of glyphosate at either 5.6 or 56 mg/kg, over 70% of the administered dose was eliminated within 24 hours. After a single oral dose of glyphosate (10 or 1,000 mg/kg), greater than 90% of the dose was excreted within 48 hours of treatment and less than 1% of the dose remained in the body after 120 hours. The elimination phase suggests a two compartment model. In the National Toxicology Program (NTP) study, the α phase half-life at the 5.6 mg/kg dose was about 0.5 hours and the β phase half-life was about 13 hours. In the Monsanto study at the 10 mg/kg dose level, the half-life for the α phase was 5.9 to 6.2 hours and for the β phase was 79 to 106 hours. Biliary excretion occurred to a minor extent, and less than 1% of the administered dose was expired as CO_2 (Monsanto, 1973 as cited by WHO, 1994).

In soils, glyphosate is readily degraded by soil microbes to inorganic constituents, including carbon dioxide and phosphate. In water, glyphosate does not degrade readily. No appreciable degradation of glyphosate was observed in water via chemical, microbiological or photolytic processes for 78 days (Anton *et al.*, 1993).

TOXICOLOGY

Toxicological Effects in Animals

Acute Effects

The acute lethal dose (LD_{50}) of glyphosate in various species by different routes is given in Table 2. Glyphosate has very low toxicity by the oral and dermal routes, partly due to its limited absorption. It is significantly more toxic by the intraperitoneal (ip) route. The reported toxic effects following acute exposure were hyperemia, severe stress, accelerated breathing and occasional asphyxial convulsion.

Table 2. Acute Toxicity of Glyphosate in Experimental Animals (NTP, 1992)

Species	**Administration mode**	**LD_{50} (mg/kg bw)**
Rat	oral	4873
Rat	ip	235
Mouse	oral	1568
Mouse	ip	130
Rabbit	oral	3800

Dermal and Ocular Effects

In a number of eye irritation studies in rabbits, a slight eye irritation was observed which was reversible. Severe irritation, erythema, edema and necrosis have been reported in a guinea pig dermal study. However, no dermal sensitization was observed in response to a challenge dose (DHS, 1989).

Subchronic Effects

Glyphosate (purity 98.7%) was administered in the diets of CD-1 mice for 90 days at levels of 5,000, 10,000 or 50,000 ppm (equal to 940, 1,890 and 9,710 mg/kg-day in males and 1,530, 2,730 and 14,860 mg/kg-day in females). The authors concluded that the NOAEL was 10,000 ppm. Liver weights were increased at 10,000 and 50,000 ppm and growth retardation and increased organ weights of brain heart and kidney were observed at 50,000 ppm (Monsanto, 1979 as cited by WHO, 1994).

In a 90-day study, Sprague-Dawley rats were administered glyphosate at 1,000, 5,000 or 20,000 ppm in the diet (equal to 63, 317 and 1,267 mg/kg-day in males and 84, 404 and 1,623 mg/kg-day in females) there were no toxic effects observed. The NOAEL from this study was 20,000 ppm (1,267 mg/kg-day) (Monsanto, 1987 as cited by WHO, 1994).

Glyphosate was administered in the diets of 10 F344N rats or B6C3F1 mice per sex per dose for 13 weeks at concentrations of 0, 3,125, 6,250, 12,500, 25,000 or 50,000 ppm. Ten additional rats per sex were included for evaluation of hematology and clinical pathology parameters (NTP, 1992). In rats, reduced weight gain was observed in males in the 25,000 and 50,000 ppm groups. The final body weight of these males was about 18% less than controls. In female rats, only a slight (5%) reduction in body weight was observed at the highest dose level. In males, there were slight increases in relative weights of liver at ≥ 3,125 ppm, kidney and testes at ≥ 25,000 ppm and a decrease in thymus weight at 50,000 ppm. Of the hematological parameters, there was a mild increase in hematocrit and red blood cell (RBC) count at ≥ 12,500 ppm, hemoglobin ≥ 25,000 ppm and platelets at 50,000 ppm. In female rats, significant increases were observed in lymphocytes at ≥ 25,000 ppm and platelet counts ≥ 3,125 ppm, white blood cells (WBC) at ≥ 12,500 ppm, mean corpuscular hemoglobin (MCH) at 50,000 ppm and mean corpuscular volume (MCV) at 50,000 ppm. The changes in clinical chemistry parameters included an increase in alkaline phosphatase at ≥ 6,250 ppm in male and at ≥ 12,500 ppm in female rats. A significant decrease (20%) was observed in sperm counts in the 25,000 and 50,000 ppm dose groups. The histopathological changes found were cytoplasmic alterations in the parotid and submandibular salivary glands,

consisting of basophilic changes and hypertrophy of acinar cells. Because the effects on the salivary glands were observed at all dose levels, no NOAEL was identified.

In mice, reduced weight gains were observed at the highest dose level only. Increased organ weights of heart, kidney, liver, thymus and testes were not dose-dependent and were not considered compound-related. No effects were observed on sperm motility. Pathological changes in salivary glands were similar to rats but were not observed at the lowest dose level of 3,125 ppm in the diet (equal to 507 mg/kg-day in male and 753 mg/kg-day in female mice). Therefore, the NOAEL for glyphosate in mice appears to be 507 mg/kg-day. The salivary gland lesions observed were similar to those which could be induced by the β-adrenergic agonist isoproterenol and could be partially ameliorated with the β-adrenergic antagonist propanolol, suggesting that glyphosate may be acting as a weak adrenergic agonist.

Glyphosate (96%) was administered orally by capsule at 0, 20, 100 or 500 mg/kg-day to six beagle dogs per sex per group for 52 weeks. No adverse effects were identified in this study. The NOAEL is therefore greater than 500 mg/kg-day (Monsanto, 1985).

In a dermal study, glyphosate at levels of 100, 1,000 or 5,000 mg/kg-day was applied to shaven intact or abraded skin of rabbits for six hours/day, five days/week for three weeks. At the high dose, a slight erythema and edema in intact and abraded skin and a decrease in serum lactic dehydrogenase was observed in both males and females. (IRDC, 1982 as cited by WHO, 1994).

In a four-week inhalation study with a 1:3 aqueous dilution of Roundup formulation, rats were exposed to 50, 160 and 360 mg/m^3 of the diluted formulation as an aerosol spray for six hours/day, five days/week. The mass median aerodynamic diameter of the test material ranged from 1.8 to 2.7 μm. There was a slight increase in irritation of nasal turbinates, trachea and lungs in the high dose group females compared to controls (Monsanto, 1983 as cited by WHO, 1994).

Chronic Effects and Carcinogenicity Studies

Rat

Glyphosate (98.7%) was administered to Sprague-Dawley rats (50 per sex per group) for 24 months at 0, 60, 200 and 600 ppm (equal to approximately 0, 3.05, 10.3 or 31.5 mg/kg-day for male and 3.5, 11 or 34 mg/kg-day for female rats). The systemic NOAEL for this study was 31.5 to 34 mg/kg-day. There was a statistically significant increase in interstitial cell tumors of the testes in the high dose group when compared with the concurrent controls. However, this was considered not compound-related because it was within the range of historical controls (Bio/Dynamics Inc., 1981a as cited by WHO, 1994).

Glyphosate (purity 96.5%) was administered to Sprague-Dawley rats (60 per sex per group) for 24 months at concentrations of 0, 2,000, 8,000 or 20,000 ppm. An additional 10 rats per sex per group were included for one year interim sacrifice. The NOAEL for this study was 8,000 ppm (equal to 410 mg/kg-day). There was a significant increase in the incidence of basophilic degeneration of the posterior subcapsular lens capsule fibers in the eye of male rats in the highest dose group. Liver weight was also increased in male rats of the highest dose group. There was an increase in the incidence of pancreatic islet cell adenomas in male rats in the lowest dose group.

No dose-response was observed for this effect. C-cell adenomas in thyroid were slightly increased in male and female rats in the mid and highest dose groups (Monsanto, 1990b as cited in Fed. Reg., 1997).

Mice

Glyphosate (purity 99.7%) was administered for 24 months in the diet of 50 CD-1 mice per sex per dose at concentrations of 0, 1,000, 5,000 or 30,000 ppm (approximately equal to 0, 150, 814 and 4,841 mg/kg-day in male and 0, 190, 955 and 5,874 mg/kg-day in female mice). The NOAEL was 5,000 ppm. There was a slight decrease in the mean body weights of male mice in the highest dose group. Histopathological changes included an increased incidence of central lobular hepatocyte necrosis in male mice in the highest dose group. Chronic interstitial necrosis and proximal tubule epithelial cell hyperplasia in the urinary bladder was observed in female mice in the mid and highest dose groups (Bio/Dynamics Inc., 1983).

Genetic Toxicity

Glyphosate was negative in various *in vivo* and *in vitro* test systems evaluating gene mutation, chromosomal aberration and DNA damage (Cal/EPA, 1992).

Teratogenicity

Glyphosate (purity 98.7%) was administered by gavage at levels of 0, 300, 1,000 or 3,500 mg/kg-day to female COBS CD rats on days 6 to 19 of gestation. Developmental toxicity was seen only at dosages which caused substantial maternal toxicity. The maternal and developmental toxicity NOAELs were 1,000 mg/kg-day (IRDC, 1980a).

Glyphosate technical (98.7%) was administered orally to 16 Dutch Belted rabbits per dose at 0, 75, 175 or 350 mg/kg-day on days 6 to 27 of gestation. The maternal NOAEL in this study was 175 mg/kg-day. Two dams died at the mid dose from unknown causes. At the highest dose, there was treatment-related diarrhea, nasal discharge and high mortality (IRDC, 1980b as cited by WHO, 1994).

Reproductive Toxicity

Glyphosate, (purity 98.7%) was administered in the diet to CD rats at levels of 0, 3, 10 or 30 mg/kg-day for three successive generations. There was an increased incidence of unilateral renal tubular dilation in the male pups of the F_{3b} generation at the highest dose. The NOAEL for reproductive effects was 30 mg/kg-day. The systemic NOAEL was 10 mg/kg-day (Bio/Dynamics Inc., 1981b as cited by WHO, 1994).

In a two-generation study, glyphosate was administered to CD rats at levels of 0, 2,000, 10,000 or 30,000 ppm in the diet (equal to 0, 100, 500 and 1,500 mg/kg-day) for 11 weeks before they were mated to produce the F_1 generation. The F_1 animals and pups had reduced body weights (8 to 11%) in the highest dose group. Sporadically reduced body weights were also observed in the mid-dose group, but they were not considered to be compound-related. The NOAEL in this study was 10,000 ppm in the diet (500 mg/kg-day) (Monsanto, 1990a).

Special Studies

Yousef *et al*. (1995) studied the effects of carbofuran and glyphosate on semen characteristics in rabbits. Carbofuran or glyphosate was given orally in gelatin capsules to four male New Zealand white rabbits per dose at levels of 0, 1/100 LD_{50} or 1/10 LD_{50} daily for six weeks. Actual LD_{50} values were not given in the paper. A preliminary six-week evaluation period was followed by a six-week treatment period, then followed by a six-week recovery period without pesticide administration. The animals were weighed and semen collected weekly throughout the 18-week period. Semen volume, fructose osmolarity, sperm concentration and live, dead and abnormal spermatozoa were evaluated. The authors concluded that pesticide treatment reduced body weight, libido, ejaculate volume and sperm concentration and increased abnormal and dead sperm. at both dose levels. The adverse effects continued into the recovery period.

Toxicological Effects in Humans

Talbot *et al*.(1991) reported a number of cases of acute intoxication (suicide attempt) with herbicides containing glyphosate. The reported acute symptoms were: sore throat, dysphagia, gastrointestinal hemorrhage and erosion of the gastrointestinal tract. Other less commonly affected organs were: lung, liver, kidney and the central nervous system. The estimated amount of Roundup (41%) ingested by non-survivors was 184 +/- 70 mL (range 85 to 200 mL). Most of the deaths occurred within hours of ingestion of the herbicide. In another study, Tominack *et al.* (1991) estimated a dose of 120 +/-112 mL in survivors and 263 +/-100 mL for non-survivors of suicide attempts. The most common reported symptoms in this study were irritation of mucous membrane and gastrointestinal tract. Minor reported effects were pulmonary dysfunction, metabolic acidosis, hypotension, leukocytosis and fever. The high concentrations of both glyphosate and its constituent surfactant in the formulated product which were encountered in the suicide cases are not anticipated in drinking water.

In a sensitization study in 204 volunteers with undiluted Roundup®, no effects were observed. Also, controlled studies of farm workers suggest no effects (WHO, 1994). However, some glyphosate products are in toxicity category I and II for primary eye irritation and dermal irritation. Glyphosate is considered a leading cause of eye and skin irritation in mixer/loader/applicators in California (U.S. EPA 1993).

Mechanism of Action

In plants, glyphosate inhibits the shikimic acid pathway of aromatic amino acid synthesis, photosynthesis, plant respiration, plant nucleic acid synthesis and the metabolism of phenolic compounds (reviewed by Eldon and Oehme, 1992). The primary mode of herbicidal action is blockade of the shikimic acid pathway, which exists only in plants and microorganisms and not in mammals (Malik *et al.*, 1989). In animals, mechanisms of toxic action have not been fully elucidated. A reduced respiratory control ratio, enhanced ATPase activity and stimulated oxygen uptake rate were observed in liver mitochondria obtained from rats given glyphosate. Based on these results, the authors suggested that these toxicological effects may be primarily due to the uncoupling of oxidative phosphorylation (Olorunsogo *et al.*, 1979). Further, it was suggested that glyphosate uncoupling effects may be due to its ability to act as a chelator and a mild protonophore (Olorunsogo, 1990).

DOSE-RESPONSE ASSESSMENT

Carcinogenic Effects

In 1985, glyphosate was classified as a Group C carcinogen (possible human carcinogen) based on an inadequate rat carcinogenicity study (high dose less than the maximum tolerated dose) and an equivocal renal tumor response in a mouse carcinogenicity study. U.S. EPA re-examined the mouse renal tumor slides and changed the glyphosate classification to Group D (not classified as to human carcinogenicity) in 1986. However, U.S. EPA required the registrant to repeat the rat study because of the equivocal results. Following review of the new rat study, U.S. EPA's peer review committee classified glyphosate as a Group E carcinogen (evidence of noncarcinogenicity) because the tumors observed (pancreatic islet and thyroid C cell adenomas in rats and renal epithelial cell hyperplasia in mice) were not considered to be compound-related and the studies of glyphosate genotoxicity were negative (Fed. Reg., 1997). Therefore , no dose-response assessment was conducted for glyphosate carcinogenicity in developing a PHG.

Noncarcinogenic Effects

In the absence of adequate human data, a reference dose (RfD) is generally calculated by U.S. EPA from the most sensitive endpoint in a long-term mammalian toxicology study. An RfD, as defined by the U.S. EPA, is an estimate of a daily exposure to the human population that is likely to be without appreciable effect. It is calculated by dividing a NOAEL by an uncertainty factor (UF). A factor of 100 is used as the default, representing one factor of 10 to account for the extrapolation of animal data to humans and another factor of 10 to account for human variability in susceptibility to toxic chemicals.

Reference Dose

The U.S. EPA RfD of 0.1 mg/kg was based on the three-generation rat reproduction study (Bio/Dynamics Inc., 1981b) with a NOAEL of 10 mg/kg and an UF of 100. The NOAEL was based on renal tubular dilation in F_{3b} pups at the next higher dose of 30 mg/kg. This RfD is the basis for U.S. EPA's drinking water equivalent levels (U.S. EPA, 1992) and the current Maximum Contaminant Level Goal (MCLG) and MCL (U.S. EPA, 1996) of 700 ppb. In its risk assessment, DHS used the same RfD and critical study in calculating the PMCL (DHS, 1989).

In a more recent two-generation rat reproduction study (Monsanto, 1990a), no histopathological effects on kidneys of F_{2b} pups were observed at a much higher dose level (500 mg/kg). The NOAEL from this study was 10,000 ppm (500 mg/kg-day) based on decreased body weights and soft stool in the next higher dose group. Therefore, the results from this study suggest that renal effects in the three-generation rat reproduction study were not compound-related. In addition, other toxicity studies do not support that the renal effects are compound-related.

U.S. EPA's most current RfD of 2 mg/kg (Fed. Reg., 1997) is based on a maternal NOAEL of 175 mg/kg and an UF of 100 in a rabbit study (IRDC, 1980b). The NOAEL is based on maternal mortality at the next higher dose. A recent review of glyphosate considered the rabbit teratology study with a NOAEL of 175 mg/kg-day as the appropriate basis for toxicological evaluation in humans (WHO, 1994). U.S. EPA Office of Pesticide Program's RfD of 2 mg/kg-day is also based

on this study. We consider that the rabbit teratology study with a NOAEL of 175 mg/kg-day is an appropriate study for PHG determination.

CALCULATION OF PHG

The following general equation for noncarcinogenic endpoints is used for calculating a public health-protective concentration (C, in mg/L) for glyphosate in drinking water:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L/day} = mg/L$$

where,

NOAEL	=	No-observed-adverse-effect-level (175 mg/kg-day)
BW	=	Body weight for an adult female (60 kg).
RSC	=	Relative source contribution of 20% (0.2)
UF	=	Uncertainty factor of 1,000 (10-fold for inter-species variation, 10-fold for human variability and 10-fold for extrapolation from short-term to long-term exposure)
L/day	=	Volume of water consumed daily for an adult (2 L/day)

This calculation is based on the assumption that a 60 kg adult female (the endpoint is related to toxicity in women) consumes two liters of water per day and the glyphosate contribution from water is 20%. The relative source contribution of 20% is the same as U.S. EPA's default value for organic chemicals.

Therefore,

$$C = \frac{175 \text{ mg/kg-day} \times 60 \text{ kg} \times 0.2}{1{,}000 \times 2 \text{ L/day}}$$

$$= 1.05 \text{ mg/L} = 1 \text{ mg/L (rounded)} = 1{,}000 \text{ ppb.}$$

OEHHA calculates a PHG of 1,000 ppb for glyphosate in drinking water. This PHG is higher than U.S. EPA's MCL of 700 ppb.

RISK CHARACTERIZATION

Glyphosate is relatively low in toxicity. In most of the short-term and long-term toxicity studies, reduced body weight, increased liver weights, and cytoplasmic changes in the parotid and submandibular salivary glands were observed. These effects were observed at ≥ 350 mg/kg-day dose levels. Glyphosate is a Group E carcinogen (evidence of no carcinogenic effects). It is not a teratogen or a reproductive toxicant, but maternal death was observed at 350 mg/kg-day in the critical rabbit teratology study. The increased mortality in rabbits may be due to species specific sensitivity to glyphosate and an increase in sensitivity during pregnancy. Mortality was not observed at much higher dose levels in chronic studies in rats and mice. The other endpoint of concern is reduced sperm concentration as observed in the subchronic study of Yousef *et al.* (1994). In rabbits in this study, reduced sperm concentrations were observed at both the levels

tested and therefore no NOAEL was identified. This study had only four rabbits per dose group and the actual LD_{50} value on which the dose levels were based was not specified. Therefore, the use of these data would add more uncertainty to the risk assessment. However, significant reduction in the sperm concentration (20%) was also identified in the NTP (1992) study at the high doses of 1,678 and 3,393 mg/kg-day in rats. This toxic effect in the male reproductive system warrants further study.

There are no human data on which to develop a PHG for glyphosate. Therefore, the PHG derived for glyphosate is based on laboratory animal studies. In obtaining a PHG from animals for application to humans there is an inherent assumption that the data obtained in animals are relevant to humans. To account for inter- and intra-species variation, a UF of 100 is used for calculating the PHG. An additional UF of 10 is added because of the use of a systemic endpoint (diarrhea, mortality) from a short-term exposure study (teratology). The toxicity data for glyphosate are adequate and the observed NOAEL is high (175 mg/kg). It should be noted that toxicity tests have been conducted in young and developing laboratory animals and no extra sensitivity, relative to adults, has been observed. No other more susceptible subgroups have yet been identified in laboratory or epidemiological studies. Also, there are no reports in the available literature dealing with the interaction of glyphosate with other chemicals

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